Intrauterine fetal death during COVID-19 pregnancy: Typical fetal heart rate changes, coagulopathy, and placentitis

Maya Kato[1] ⓘ, Kyohei Yamaguchi[1] ⓘ, Yuka Maegawa[1], Shihoko Komine-Aizawa[2] ⓘ, Eiji Kondo[3] ⓘ and Tomoaki Ikeda[3]

[1]*Department of Obstetrics and Gynecology, Mie Central Medical Center, Mie, Japan*
[2]*Division of Microbiology, Department of Pathology and Microbiology, Nihon University School of Medicine, Tokyo, Japan*
[3]*Department of Obstetrics and Gynecology, Mie University, Mie, Japan*

Abstract

Although various perinatal outcomes in coronavirus disease 2019 (COVID-19) pregnancies have been reported, the fetal and neonatal consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection remain unclear. Several reports of miscarriages and stillbirths have been recorded, but vertical transmission by SARS-CoV-2 is considered very rare, and the cause remains unknown. We report a case of a 22-year-old uncomplicated Japanese woman infected with SARS-CoV-2 during the second trimester, resulting in intrauterine fetal death due to placental insufficiency associated with COVID-19 placentitis. This report emphasizes the importance of longitudinal assessment of fetal well-being by fetal heart rate monitoring and early detection of maternal coagulation dysfunction representing SARS-CoV-2 inflammation to manage COVID-19 in pregnancy.

Key words: coronavirus disease 2019, fetal heart rate monitoring, intrauterine fetal death, placentitis, pregnancy, severe acute respiratory syndrome coronavirus 2.

Introduction

Since the novel coronavirus disease 2019 (COVID-19) pandemic, various effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on both mother and fetus have emerged. Accumulated data describe adverse perinatal outcomes, such as premature rupture of membranes, preterm labor, intrauterine growth restriction, intrauterine fetal distress and death, and neonatal death.[1,2] However, the potential effects on fetal and neonatal outcomes are poorly understood, and vertical transmission to the fetus remains debated.[3] Furthermore, a paucity of reports discuss changes in fetal heart rate (FHR) monitoring during COVID-19 pregnancy and its association with SARS-CoV-2 infection.

Herein, we present a case of intrauterine fetal death characterized by typical hypoxic changes in the FHR and coagulopathy in the second trimester of a COVID-19 pregnancy, presumed to be caused by placental insufficiency due to SARS-CoV-2 placentitis.

Case Report

We report a case of a 22-year-old gravida 2, para 1 Japanese woman, whose pregnancy course was uncomplicated with no relevant medical history, and her body mass index was 19 kg/m². SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) was performed using a nasopharyngeal swab at 21 weeks and 3 days of gestational age since she had close contact with her COVID-19-positive husband. She was diagnosed with COVID-19 and referred to our hospital at 21 weeks and 4 days (day 0).

TABLE 1 Patient's laboratory test results

	Normal range	21 weeks 4 days, day0	22 weeks 1 day, day4	22 weeks 4 days, day7	22 weeks 5 days, day8
White blood cell count (/μL)	3000–10 000	6910	2600	3480	4260
Lymphocyte (/μL)	1000–3500	1070	390	1220	1060
Platelets (×10^4/μL)	21.7–26.4	18.5	8.6	7.5	7.9
LDH (U/L)	135–225	228	282	467	425
CRP (mg/dL)	<1	0.19	2.52	1.13	0.9
Fib (mg/dL)	248–506			159	172
FDP (μg/mL)	<15	1.7	50	21.1	6.4
D-Dimer (μg/mL)	0.16–1.7	1.2	13.3	14.6	8

Abbreviations: CRP, C reactive protein; Fib, fibrinogen; LDH, lactate dehydrogenase.

At the time of admission, she was asymptomatic, with a body temperature of 37.1°C, pulse rate of 75 bpm, blood pressure of 94/66 mmHg, respiratory rate of 18 bpm, and SpO2 of 98% on room air. Blood test results and chest radiography were normal. Obstetric ultrasound examination showed no fetal anomalies, normal amniotic fluid volume with fetal body movements, and an estimated fetal weight of 381 g (−0.9 SD). The FHR was assessed daily by Doppler and remained within normal limits.

On day 2 (21 weeks and 6 days), her body temperature was elevated to 38.5°C with mild headache and fatigue; however, no significant changes in blood pressure, heart rate, and respiratory conditions were observed.

On day 4 (22 weeks and 1 day), she achieved fever resolution, and her general condition remained unchanged; nevertheless, plasma fibrin degradation product (FDP) and D-dimer levels increased to 50.0 and 13.3 μg/mL, respectively. White blood cell count and platelets levels also decreased to 2600/μL and 8.6 × 10^4/μL, respectively. Blood test results are presented in Table 1. Meanwhile, continuous intravenous infusion of 10 000–15 000 units of heparin was initiated to prevent thrombosis. FHR changes in the cardiotocography (CTG) revealed normal variability with acceleration (Figure 1a).

On day 5 (22 weeks and 2 days), FHR monitoring showed recurrent late deceleration with normal variability, and the patient was aware of fetal movements (Figure 1b). However, on day 6 (22 weeks and 3 days), she noticed a decrease in fetal movement, and FHR monitoring demonstrated baseline tachycardia (165 bpm) with minimal variability (Figure 1c).

(a) 22w1d
Normal variability with acceleration

(b) 22w2d
Recurrent late decelerations with normal variability

(c) 22w3d
Baseline tachycardia with minimal variability

(d) 22w4d
Normal baseline but loss of variability with recurrent late decelerations
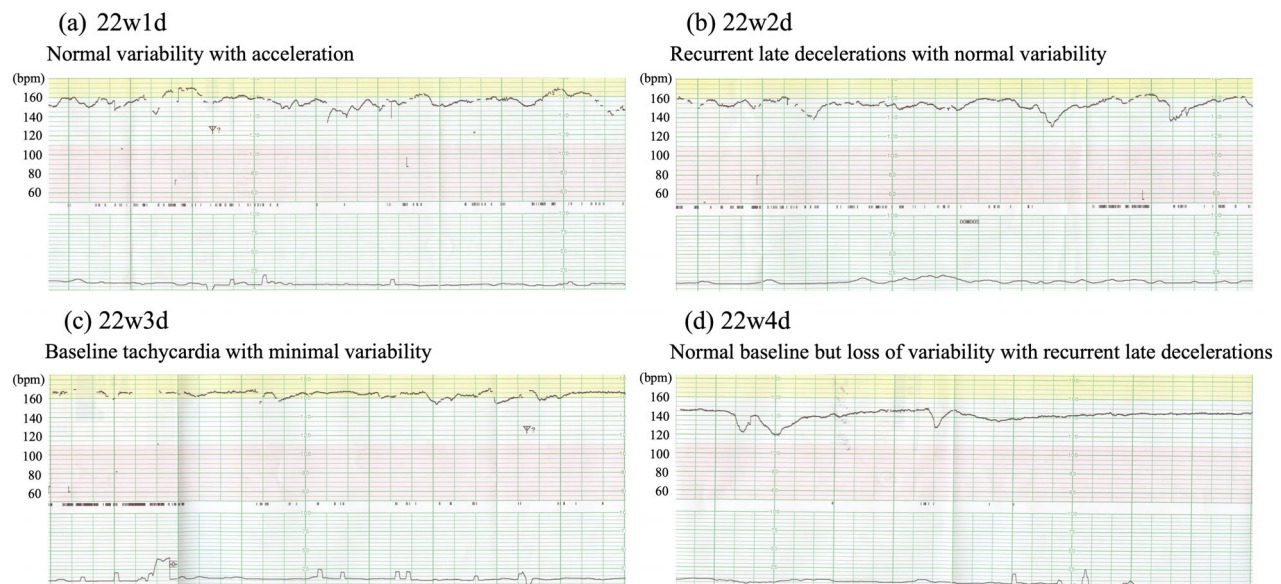
FIGURE 1 Fetal heart rate changes in the cardiotocography trace
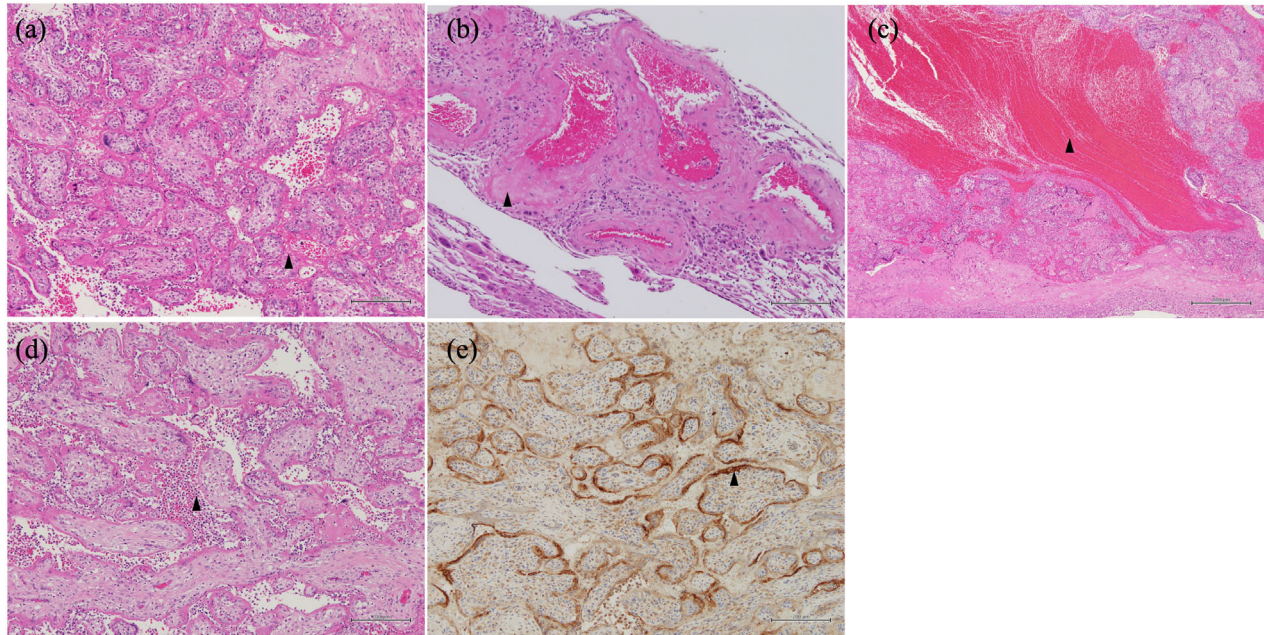
FIGURE 2 Placental pathology. (a) Perivillous fibrin deposition (×100). (b) Maternal arteriole with atherosis (×100). (c) Intervillous thrombus (Zahn lines) (×40). (d) Intervillositis with inflammatory cells in the intervillous space (×100). (e) Immunohistochemistry for SARS-CoV-2 protein showing positivity of the syncytiotriphoblast (×100)

On day 7 (22 weeks and 4 days), she reported the absence of fetal movements, and subsequent FHR monitoring showed loss of variability with recurrent late decelerations (Figure 1d). Transabdominal ultrasonography did not reveal any fetal breathing movements, gross body movements, or tone. Successive CTG trace are shown in Figure S1a–d.

After obtaining informed consent from the parents, they chose expectant management of the pregnancy due to the extreme prematurity of the fetus. We confirmed intrauterine fetal death the next day, and a stillborn male fetus weighing 384 g was delivered vaginally in the pelvic position. Furthermore, there was no evidence of external malformation, and the placenta weighed 120 g, with deciduous membrane necrosis, arteriosclerosis, and villous edema. Microscopic evaluation of the placenta revealed there was constriction of the intervillous space and extensive intervillous fibrin deposition (Figure 2a), thickening of the wall of the spiral artery in the decidual membrane indicating atherosis of the maternal arteriole (Figure 2b), an intervillous thrombus displaying Zahn lines (Figure 2c), and an intervillositis with numerous inflammatory cells in the intervillous space (Figure 2d). Moreover, immunohistochemistry for the SARS-CoV-2 spike protein showed strong positive staining in syncytiotrophoblasts (Figure 2e).

The RT-PCR test result from a dead neonatal nasopharyngeal swab was positive. SARS-CoV-2 RNA was detected in the cord blood (124 166 copies/mL; QIAamp Viral RNA Mini) and placental tissue (67 122 576 copies/μg; ReliaPrep™ RNA Miniprep Systems). However, no consent was obtained from the family for fetal autopsy.

Her blood coagulation abnormality was resolved 2 days postdelivery. Computed tomography (CT) of the chest and pelvic region of the patient revealed no venous thromboembolism (VTE), and she was discharged on day 2 postpartum without complications.

Discussion

Our patient had two important clinical implications. (1) SARS-CoV-2 infection can cause placentitis, which may cause serious fetal hypoxia, leading to death even in an uncomplicated asymptomatic pregnant woman. Daily FHR monitoring is essential for the longitudinal assessment of fetal well-being. (2) Placentitis with histological characteristics, such as perivillous fibrin deposition, maternal arteriole with atherosis, intervillous thrombus, and intervillositis, is presumed

to be caused by maternal coagulation dysfunction in COVID-19-infected pregnant women.

Since the COVID-19 pandemic, various adverse perinatal outcomes have been reported, including increased risks of miscarriage, preterm birth, preeclampsia, and stillbirth.[4] Nevertheless, the reasons underlying the association with adverse outcomes remain unclear, and appropriate assessment, especially on fetal well-being in COVID-19 pregnancy, has not been fully discussed.

FHR monitoring, which can reflect fetal autonomic nervous function and oxygenation, is mainstream for fetal physiological assessment. Only a few reports describing COVID-19 pregnancy and its association with changes in FHR patterns are available.[5,6] Gracia-Perez-Bonfils et al.[5] retrospectively analyzed 12 CTG traces and reported that all fetuses showed an increased FHR baseline in addition to the absence of accelerations, and most fetuses demonstrated late or prolonged decelerations. Sinaci et al.[6] prospectively evaluated 224 CTG traces on a single pregnancy of ≥32 weeks and found that an increased FHR baseline was the most obvious change and had no strong association with other FHR patterns or CTG categories. They suggested that fetal tachycardia likely represents the fetal response to maternal pyrexia, inflammatory mediators, and cytokine storms. Perinatal outcomes were favorable despite the abnormal CTG traces observed in COVID-19 pregnancies.

In the present case, serial CTG traces showed recurrent late decelerations, subsequent decreased baseline FHR, and loss of variability followed by tachycardia, typically representing Hon's FHR evolution pattern.[7] The FHR is characterized by an exacerbated fetal hypoxic situation due to an insufficient balance between the fetal oxygen demand and its supply to the fetus through the placenta.

COVID-19 may cause a thrombotic condition due to inflammation, platelet activation, and endothelial dysfunction.[8] Since pregnancy is a physiologically hypercoagulable state, the risk of coagulopathy and thromboembolism is increased in pregnant women with COVID-19, and a similar pathological change caused by COVID-19 might occur in the placenta.

There have been various reports of COVID-19 infection and placental pathology to date. Although no consistent pathological findings have been obtained, an association with maternal and fetal vascular abnormalities has been recognized.[9] Recently, Sharps et al.[10] analyzed 20 studies reporting placental histopathology infected by SARS-CoV-2 in the third trimester. They reported that maternal vascular malperfusion and fetal vascular malperfusion (46% and 35.3% of cases, respectively) were the two main findings following perivillous fibrin deposition or inflammatory changes occurring in <10% of cases. In our case, in addition to pathological findings similar to the existing reports described above, immunohistochemistry revealed positivity for SARS-CoV-2 spike protein in the syncytiotrophoblast. Moreover, the nasopharyngeal PCR results of the dead neonate were positive, and a significant amount of viral RNA was detected in the cord blood and placental tissue. Although some reports indicate that SARS-CoV-2 mRNA by in situ hybridization and spike protein by immunohistochemistry are detected in the placenta of pregnant women with COVID-19, and evidence of vertical transmission of SARS-CoV-2 has emerged,[11] the incidence is very rare. There remains a paucity of evidence to support this. During pregnancy, the placenta serves as an anatomical barrier that acts as the first line of defense to avoid the transmission of pathogens from mother to fetus.[12] This mechanism of fetoplacental protection known as the placental barrier partly explains that transmission of SARS-CoV-2 is unlikely to occur.

SARS-CoV-2 placentitis is a rare complication of COVID-19 pregnancy; however, our placental findings support the concept that inflammation is directly related to viral infection and represents placentitis.[13]

Altogether, the typical Hon's FHR evolution pattern was mainly due to uteroplacental insufficiency caused by significant placentitis with multiple micro-thromboses of SARS-CoV-2 infection.

Despite the increasing evidence on COVID-19 and pregnancy that has been discovered, adverse perinatal outcomes, especially in early pregnancy, are not well understood. Some reports have described an association between the abovementioned placental pathologies and miscarriage, intrauterine fetal death, or fetal distress.[14,15] Pregnant women suffer from obesity and glucose intolerance, which are presumably significant risks for SARS-CoV-2 infection.

Since its emergence in December 2019, SARS-CoV-2 has constantly mutated with different virulence factors. Currently, the global spread of COVID-19 variants of concern (VOCs) is attracting attention. This case occurred during the delta-variant pandemic period in September 2021. It is unknown whether placentitis is less likely to occur because of other variants of SARS-CoV-2.

In conclusion, we report the case of an uncomplicated pregnant woman infected with SARS-CoV-2 in

the second trimester, subsequently resulting in intrauterine fetal death due to COVID-19 placentitis. To determine the appropriate timing of intervention and delivery, pregnant women with COVID-19 should be carefully assessed using longitudinal FHR monitoring and maternal coagulation function.

Acknowledgments

Conflict of interest

The authors declare no conflict of interests for this article.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supplemental Fig. 1-1 Successive Fetal heart rate changes in the cardiotocography trace.

Supplemental Fig. 1-2 Successive Fetal heart rate changes in the cardiotocography trace.